UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/331,375	12/03/1999	CHARLES M. COHEN	CIBT-P01-519	1578

28120 7590 06/03/2003

ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/331,375	COHEN ET AL
Examiner	**Art Unit**
Regina M. DeBerry	1647

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *2-4,21-23,25-27 and 30* is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,5-20,24,28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-30* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other

Status of Application, Amendments and/or Claims

Applicant has requested reconsideration in view of the remarks stated in the response (25 March 2003, Paper No. 18).

Reference exhibits A, B and C have been received.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Abstract

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required. The basis for this rejection is set forth at page 2 of the previous Office Action (20 December 2002, Paper No. 17). Applicant has stated that a copy of the abstract page (page 94 of the specification as originally filed) has been submitted. The abstract page has not been received.

Claim Rejections - 35 USC § 112, Enablement

Claims 1, 5-20, 24, 28 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis for this rejection is set forth at pages 3-5 of the previous Office Action (20 December 2002, Paper No. 17).

Applicant states that the test for enablement is whether one of skill in the art could practice the claimed invention without undue experimentation. Applicant maintains that the specification need not disclose what is well known to those skilled in the art and

preferably omits that which is well known to those skilled and already available to the public. Applicant asserts that the specification teaches the instant invention. Applicant cites pages in the instant specification. Applicant states that Fields (WO 95/14079), cited as prior art in the last Office Action confirms that direct injection can be used to introduce various precursor cells directly into the heart of experimental animals. Applicant states that those skilled in the art are well equipped with routine techniques for accessing a heart *in vivo* and that an attending physician can easily determine an appropriate amount and duration of treatment in view of the scope of the claims and the teachings of the instant specification, which is accomplished using no more than routine procedures commonly practiced in the field.

Applicant's arguments have been fully considered but not deemed persuasive for the following reasons. The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. Lack of a working example, however is a factor to be considered, especially in a case involving an unpredictable and undeveloped art. There is a high level of unpredictability in the art regarding the instant invention. The specification states, "it has never previously been shown or suggested that treatment of myogenic precursor cells with the morphogens, morphogen inducers, agonists of morphogen receptors, or small molecule morphogenic activators is useful in promoting the proliferation and/or differentiation of myogenic precursor cells into new and functional myocardium in a morphogenically permissive environment". "Nor has it previously been shown or suggested that morphogenically-treated myogenic precursor

cells are useful in the treatment of lost or damage mammalian myocardium" (page 5, lines 1-10). Thus, one skilled in the art cannot readily anticipate the effects of the experiments. The pages cited by Applicant do not explicitly teach the subject matter to be patented, there are no working examples and there is a high level of unpredictability in the art. Furthermore, the Examiner withdrew the 102(b) rejection as being anticipated by Fields, because Applicant stated that Fields does not teach or suggest that morphogen can be used to stimulate myogenic precursor cells to proliferate/differentiate into functional myocardium, either before, after, or simultaneously with the implantation of such precursor cells into a mammal. Applicant stated that Fields is completely silent about morphogens and that the grafts in Fields are either non-proliferating, differentiated (by growing in low-serum media rather than by being in contact with a morphogen)(15 October 2002, Paper No. 16, pages 13-15).

Applicant is unable to discern the rejection "the specification does not teach the potential effects or morphogens on any kind of cells in any kind of biological activities". The rejection was made because the claims are *broadly* drawn to implanting myogenic precursor cells into a mammal at a site at risk of, or afflicted with, loss of or damage to myocardium and treating myogenic precursor cells with a morphogen to promote proliferation or differentiation. The specification fails to demonstrate that any myogenic precursor cell can be implanted into a mammal and that any morphogen can be used to promote differentiation or proliferation of said myogenic precursor cells into functional myocardium. Applicant has not provided art suggesting that any myogenic precursor cell or any morphogen can be used in the instant invention.

Applicant states that the specification teaches isolating myogenic precursor cells from skeletal muscle, embryo, and established lines. Applicant contends that the teachings of the specification clearly show that myogenic precursor cells will differentiate into functional myocardium. Applicant states that subsequent publications refute the Examiner's position. Applicant maintains that although the data is not shown, an *in vivo* experiment had been performed to support the claimed invention. Applicant submits Exhibit A (Behfar *et al.*), Exhibit B (Orlic *et al.*) and Exhibit C (Jackson *et al.*). Applicant maintains that all these working examples provide convincing post-filing evidence that myogenic precursor cells can differentiate into functional myocardium as claimed.

Contrary to Applicant's assertion, the claims are drawn to implanting a preparation of myogenic precursor cells into a mammal and treating myogenic precursor cells (either prior, simultaneously, or subsequent to implanting myogenic precursor cells) with an amount of a morphogen sufficient to promote proliferation or differentiation of myogenic precursor cells into functional myocardium. Exhibit B and Exhibit C are not applicable to the instant invention because the references are silent to treating cells with a morphogen. The Examiner will discuss Behfar *et al.* Exhibit A.

Behfar cultures murine embryonic stem cell line in medium containing low serum and leukemia inhibitory factor (LIF) obtained from LIF-D cells. Differentiation was carried out in hanging drops of differentiation medium (20% FCS without LIF) in which embryoid bodies were formed (page 1559). Behfar states that stem cells deprived of LIF, a suppressor of differentiation, lose their compact appearance and with it the potential for

mesodermal differentiation. BMP2 and TGF-B increased mRNA encoding markers in cardiac differentiation (page 1560). The specification, however, as originally filed does not teach the use of leukemia inhibitory factor or any other factor as suppressors of differentiation. The specification as originally filed does not teach specifically hanging drops or embryoid bodies as disclosed by Behfar. Furthermore, Applicant previously stated, "TGF-B is not a morphogen of the claimed invention" (15 October 2002, Paper No. 16, page 9). The specification states that myogenic precursor cell proliferation has been shown to be inhibited by TGF-B (page 16, line 25). Behfar teaches *in vitro* cardiac differentiation of stem cells grafted onto cardiomyocytes enhanced by TGF-B and BMP2. Undifferentiated stems cells carry a marker under the control of the cardiac alpha actin promotor (actinECFP). When activated, cells carrying the marker demonstrate express ECFP, thus indicating a ventricular phenotype. The specification as originally filed does not teach the co-incubation of cardiomyocytes or the engineering of precursor cells to carry a marker demonstrating a specific phenotype. The specification as originally filed does not teach how to discern if the precursor cells have a cardiac phenotype. Applicant states that it is unnecessary to determine if the precursor cells have actually turned into heart muscles, since the specification itself teaches this. Applicant cites page 33, line 6. This is not found conclusive because the page cited by Applicant does not teach the use of specific markers. Furthermore, the teachings of the specification are prophetic. As was stated above, there is a high level of unpredictability therefore, one skilled in the art cannot readily anticipate the effects of the experiments.

Lastly, the *in vivo* experiments of Behfar are not tantamount to the subject matter sought to be patented. Behfar teaches that actinECFP cells engineered to express noggin or ^KTGFBRII disrupters of TGF-B family receptor-mediated signaling were grafted into hearts of mice. ActinECFP cells engineered to express noggin or ^KTGFBRII disrupters of TGF-B family receptor-mediated signaling failed to express ECFP fluorescence 4wk post transplantation, indicating the absence of cardiac differentiation *in vivo* (page 1563). However, this is not the same as implanting a myogenic precursor cells in a mammal and treating myogenic precursor cells with an amount of a morphogen (prior, simultaneously or subsequent implantation) sufficient to promote proliferation or differentiation of said myogenic precursor cells into a functional myocardium. Behfar would need to show that injection of TGF-B or BMP specifically into the implanted graft (treatment of myogenic precursor cells with morphogen subsequent to implantation) could rescue the phenotype i.e. express ECFP.

Applicant cites page 39, lines 21-28 to show that the specification teaches how to treat precursor cells subsequent to implanting precursor cells. This is not found persuasive because the specification does not teach how one would treat precursor cells with a morphogen in a mammal after the precursor cells have been implanted. The specification fails to teach how to specifically target precursor cell once it is in the body.

Applicant uses the Behfar reference as post-filing evidence but the specification as originally filed fails to disclose and/or teach specific assays, materials, methods, etc. needed for the invention to be enabled. In addition, the Behfar reference and the instant specification, fails to teach: use of skeletal muscle satellite cells, or the actual treatment

of myogenic precursor cells with a morphogen before, during, or after implantation into a mammal and the use of osteogenic proteins or fragments of osteogenic or bone morphogenic proteins as morphogens to treat the myogenic precursor cells. The subject matter sought to be patented as defined by the claims, is not supported by an enabling disclosure. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on 9:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RMD
May 30, 2003

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600